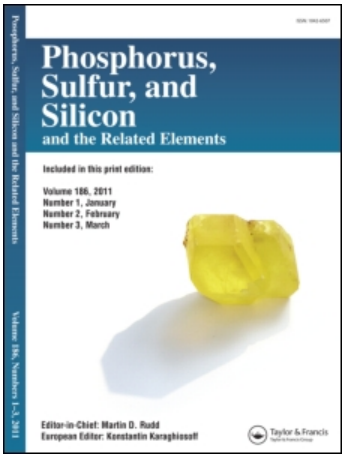

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Synthesis and stereochemical study of some biologically relevant phosphoglycerides: Dicarboxylic phosphatidylcholines and bis (diacylglycero) phosphoric acids

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SYNTHESIS AND STEREOCHEMICAL STUDY OF SOME BIOLOGICALLY RELEVANT PHOSPHOGLYCERIDES : DICARBOXYLIC PHOSPHATIDYLCHOLINES AND BIS (DIACYLGLYCERO) PHOSPHORIC ACIDS

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Abstract : Dicarboxylic (glutaryl or succinyl) phosphatidylcholines, and stereoisomeric bis (diacylglycero) phosphoric acids were synthesized. Their structures and stereoconfigurations were determinated by chemical, spectrometric and biochemical methods.

Abbreviations : BPA=bis-phosphatidic acid, BPAϕ=bis-phosphatidic acid phenyl ester, LBPA=lyso-bis-phosphatidic acid, SLBPA=semi-lyso-bis-phosphatidic acid.

Chemical synthesis of products with well defined structure and configuration is important for the study of the biological processes, especially of their stereospecificity : for instance, VAN DEENEN and DE HAAS proved by this way that phospholipase A_2 from porcine pancreas deacylates at the 2-position of acylated sn-glycero-3 phosphates but not of acylated sn-glycero-1 phosphates (1). Inversely, enzymatic reactions, which are highly stereospecific, are very useful in the determination of the stereoconfiguration of organic compounds.

We summarize here synthesis and stereochemical and biochemical studies of some phosphoglycerides : dicarboxylic phosphatidylcholines involved in the hemolysis by irradiation, and bis (diacylglycero) phosphoric acids in the Niemann-Pick lipidosis.

DICARBOXYLIC PHOSPHATIDYLCHOLINES

Ionizing radiations induce hemolysis, and the formation, in the plasma lipoproteins, of dicarboxylic phosphatidylcholines, by peroxydation of unsaturated fatty-acyl groups (2). So we synthesized a new compound of this type, the 1-acyl-2-glutaryl-sn-glycero-3 phosphorylcholine, or glutarylphosphatidylcholine (1B Fig.1) from 1-acyl-sn-glycero-3 phosphorylcholine or lysophosphatidylcholine (1A, fig. 1) and glutaric anhydride (3). Similarly we synthesized an analog : the succinylphosphatidylcholine (1C, fig. 1). Afterwards, with Prof. W. STOFFEL (KOLN), we improved the yield of acylation to about 90 % using dimethylaminopyridine as a catalyst, according to the procedure of STEGLISH (4) and GUPTA et al. (5).

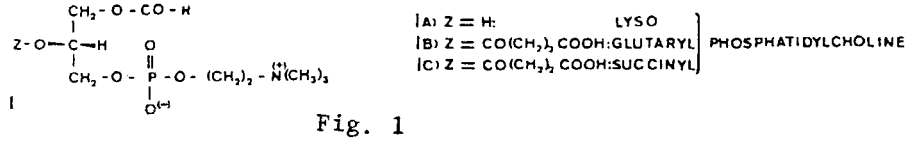

Fig. 1

These synthetic dicarboxylic phosphatidylcholines have been used for the study of the mechanism of hemolysis during irradiation. In vitro, just as lysophosphatidylcholines (IA), they induce the lysis (6) and the deformation (7) of natural membranes as erythrocytes, and model membranes as phosphatidylcholine bilayer vesicles (8).

BIS(DIACYLGLYCERO)PHOSPHORIC ACIDS (BIS-PHOSPHATIDIC ACIDS)

Some forms of the NIEMANN-PICK lipidosis and drug-induced lipidoses (9) show an accumulation of an abnormal phosphoglyceride : the bis (monoacylglycero)phosphoric acid or lyso bis-phosphatidic acid (LBPA), derivative of the bis (diacylglycero)phosphoric acid, or bis-phosphatidic acid (BPA). In these products, the glycero-P moieties may have a sn-3 (IV A, fig. 2 and 4) or the unusual sn.1 configuration (IV B, fig. 4) - (11) (12) (13). In order to get insight into the mechanism of the NIEMANN-PICK disease, we synthesized bis-phosphatidic acids of various configurations.

First we synthesized the bis (1,2-diacyl-sn-glycero-3)phosphoric acid IV A, fig. 2, essentially according to the procedure of BAER (14) : phosphorylation of the 1,2-diacyl-sn-glycerol II A by phenylphosphoryl dichloride, into the phenyl bis (1,2-diacyl-sn-glycero-3) phosphate III A, followed by hydrogenolysis into IV A (fig. 2). We proved the configuration of this latter product by its total hydrolysis with phospholipase A_2 from pig pancreas into bis (1-acyl-sn-glycero-3) phosphoric acid V A or LBPA 3.P.3' (fig. 2) (15).

With Prof. W. STOFFEL, we developed a new procedure of synthesis of bis (diacylglycero) phosphoric acids (16) based on the condensation of phosphatidic acid with a diacyl-glycerol, catalyzed by triisopropylbenzene sulphonyl chloride essentially according to KHORANA et coll. (17), ANEJA et al. (18) (fig. 3). This one-step procedure gives a better yield than the former one, and can lead to bis (diacylglycero) phosphoric acids of any configuration and containing unsaturated acyl groups.

Afterwards, radio-labelled bis-phosphatidic acids were synthesized. Bis (1,2-(1-^{14}C)palmitoyl-sn-glycero-3) phosphoric acid (^{14}C-IV A) was obtained according to fig. 2 from 1,2 (1-^{14}C)palmitoyl-sn-glycerol, which was derived from di-(1-^{14}C)palmitoyl phosphatidylcholine by hydrolysis with phospholipase C.

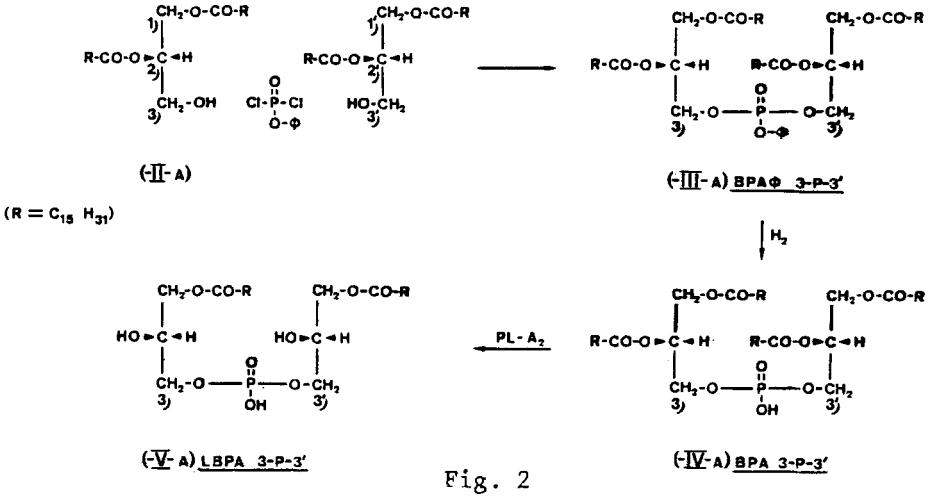

Fig. 2

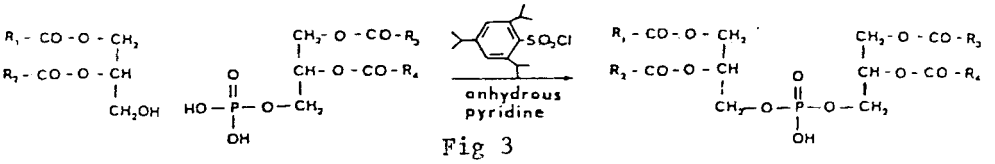

Fig 3

The bis (2,3-di(1-^{14}C)palmitoyl-sn-glycero-1) phosphoric acid (IV B) was synthesized according to the scheme fig. 4. The rac. 1,2-di(1-^{14}C)palmitoyl-glycerol (II A + II B) was obtained by hydrolysis of tri (1-^{14}C)palmitoyl-glycerol catalyzed by linase from Rhizopus Arrhizus, according to SEMERIVA et al. (19). Phosphorylation then hydrogenolysis gave a mixture of the three stereoisomers of bis-phosphatidic acids : BPA 3-P-3' (IV A), BPA 1-P-1' (IV B), BPA 3-P-1' (IV C), not isolable by T.L.C.

Phospholipase A_2-catalyzed hydrolysis of these BPA was carried out as described before (15). Owing to the specific deacylation at 2-position of sn-3-phosphoglycerides : BPA 3-P-3' (IV A) gave lyso BPA 3-P-3' (V A), BPA 1-P-1' (IV B) remained unchanged, BPA 3-P-1' (IV C) was only deacylated at the position 2 of the sn-3 moiety, giving semi-lyso BPA, SLBPA 3-P-1' (V C) ; V A, IV B and V C were well separated by TLC.

The structure and configuration of BPA 1-P-1' and SLBPA 3-P-1' were ascertained by acyl/P determination, proton NMR spectra, IR and $(\alpha)_D$ compared to BPA 3-P-3' and LBPA 3-P-3'.

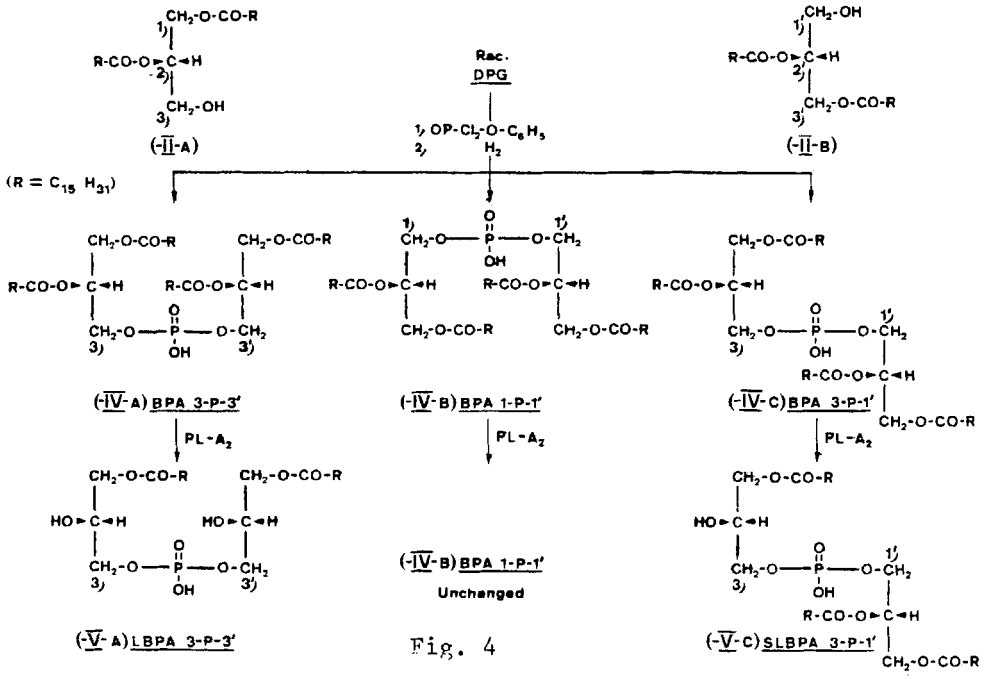

Fig. 4

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